REMARKS

THE CLAIM AMENDMENTS

Applicants have amended claims 1 and 17 to remove the claim limitation relating to the dosage form being a tablet. With this change, applicants are readdressing the Franz et al. anticipation rejection from the Office Action of August 30, 2005 (following the analysis of Mehra et al.).

THE OBVIOUSNESS REJECTION OVER MEHRA ET AL.

Claims 1-11 stand rejected under 35 U.S.C. § 103(a) as obvious over Mehra et al. (USPN 5,830,576). This rejection is respectfully traversed.

The Examiner's *prima facie* case of obviousness over Mehra et al. is based on the position that because Mehra et al. use a disintegration test to test the herbicidal tablets disclosed therein, the use of the disintegration test to determine the release profile of the claimed controlled release dosage form would have been obvious to the skilled artisan at the time of the invention. The Examiner's position is wrong for the reasons that follow.

To establish a *prima facie* case of obviousness, three criteria must be met: first, the prior art reference must teach or suggest the claimed combination; second, the Office must show that the ordinary artisan would be motivated to modify the reference or to combine the reference teachings; and third, there must be a showing that the ordinary artisan would have a reasonable expectation of success at arriving at the claimed combination based *solely* on the teachings of the cited prior art reference. *In re Rouffet,* 149 F.3d 1350, 1357 (Fed. Cir. 1998); *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991). An obviousness analysis that relies upon the applicant's disclosure rather than the prior art reference is improper as being based upon an impermissible hindsight reconstruction. *See, e.g., In re Deuel,* 51 F.3d 1551, 1558 (Fed. Cir. 1995).

With respect to the first requirement for obviousness as set forth above, the Examiner acknowledges at page 3 of the Office Action that Mehra et al. fail to teach or suggest the correlation between release profile and disintegration testing, and relating disintegration testing with selection and optimization of controlled release dosage forms. In view of the foregoing, it is unarguable that the first criteria for the *prima facie* case of obviousness is not met by Mehra et al.

With respect to the second requirement for obviousness as set forth above, the ordinary artisan would ***not*** have been motivated to use the disintegration test of Mehra et al. to test for a controlled release dosage form because there is ***no teaching or suggestion*** in Mehra at al. that the herbicidal tablets disclosed therein may be used as controlled release tablets and further, at the time of the invention (and presently as well) disintegration testing was ***not*** used to test for controlled release dosage forms. The

state of the art at the time of the invention (and presently as well) remains to use a dissolution test to test for controlled release dosage forms. In this respect, applicants remind the Examiner that the Federal Circuit has held that where an inventor achieved the claimed invention by doing what those skilled in the art suggested should not be done is *a fact strongly probative of nonobviousness*. *Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 230 USPQ 81 (Fed. Cir. 1986), *on rehearing*, 231 USPQ 160 (Fed. Cir. 1986) (emphasis added here).

To support the non-obviousness of using disintegration testing to correlate for *in vivo* release profiles of controlled dosage forms, applicants have attached to this paper Chapters 11 through 21 of the textbook Wagner, BIOPHARMACEUTICS AND RELEVANT PHARMACOKINETICS (Drug Intelligence Publications, Hamilton, IL 1971) (referred to hereinafter as Wagner), which is the primary textbook used by those of skill in the art to which the invention pertains with respect to established teachings on disintegration and dissolution testing. Also are copies of Chapter 724 of the 2000 edition of the United States Pharmacopoeia and the National Formulary ("USP-NF") and Chapters 701 and 711 of the 2001 edition of the USP-NF.

At Chapter 11 of Wagner (pages 68-69), it is explained that disintegration testing involves the agitation of a dosage form and the time required for the dosage form to break into fragments small enough for the dosage form to pass through a screen of stated mesh size; accordingly, disintegration testing tests the rate at which a dosage form is no longer intact except for small aggregates. Pages 70 and 71 of Wagner describe the progression of disintegration testing from 1950 to 1970, with the end result being the author's conclusion at page 71 (bottom of the 2nd column) that tablets tested by disintegration testing were found to be not fully available physiologically. Chapter 12 of Wagner describes the failing of the disintegration test to predict physiological availability (page 75). At page 79, Wagner describes an *in vivo/in vitro* correlation study for an enteric coated tablet using disintegration testing; at the bottom of column 2 of page 79, Wagner comes to the conclusion that there is ***not*** a direct proportionality between *in vivo* and *in vitro* disintegration times. The "inherent faults" of disintegration tests with respect to physiological availability are repeated at the beginning of Chapter 13 (page 82, second column).

At Chapter 20 (page 125 et seq.), Wagner explains the correlation of *in vitro* dissolution testing with *in vivo* drug absorption as follows:

> The rate at which a drug *dissolves* from its intact or fragmented dosage forms in the human gastrointestinal tract, or in a parenteral injection site, often partially or completely control the rate which the drug appears in blood (i.e., the rate of absorption) and the rate of urinary excretion of the drug. Results of *in vitro* rate of

> dissolution tests may often by correlated with *in vivo* results obtained with the same dosage forms.

The foregoing excerpts from Wagner clearly show that prior to the invention, disintegration testing was ***not*** considered a reliable *in vitro* determinant of *in vivo* absorption whereas dissolution testing was clearly considered a reliable *in vitro* determinant of *in vivo* absorption. As indicated in Chapter 21 of Wagner, *in vitro/in vivo* correlation specifically refers to a predictive mathematical model describing the relationship between an *in vitro* property of an extended release dosage form (i.e., the rate or extent of drug dissolution or release) and a relevant *in vivo* response, e.g., plasma drug concentration or amount of drug absorbed. Because dissolution testing has been determined to be predictive of the rate of dissolution of a dosage form within the gastrointestinal tract (see discussion set forth above), dissolution testing is the testing that is referenced for *in vitro/in vivo* correlation determination.

The foregoing discussion from Wagner demonstrates that prior to the present invention, disintegration testing was not considered suitable for testing modified release dosage forms, such as for example, controlled release dosage forms, because disintegration testing does not measure complete deaggregation of the dosage form; rather, it only evaluates tablet appearance. Because tablets may disintegrate while releasing little or no active agent, due to active agent adherence to particles in the aggregates that remain in the mesh after the test is complete, it follows that disintegration testing is not an accurate test of active agent release.

Unlike disintegration testing, which tests the rate at which a dosage form disintegrates, dissolution testing tests the rate at which a dosage form completely dissolves. As noted above, dissolution refers to the ability of a dosage form to release active agents into a medium that is deigned to adequately simulate the gastrointestinal tract. It is for this reason, the United States Pharmacopoeia and the National Foundry set dissolution requirements for all modified release dosage forms (see chapters 711 and 724) and indicate that disintegration testing is only to be used for non-modified release dosage forms (see chapter 701).

With respect to the third requirement for obviousness as set forth above, the ordinary artisan would ***not*** have a reasonable expectation of achieving the controlled release dosage form of the claimed invention by reading Mehra et al. because there is ***no*** teaching or suggestion in Mehra et al. that the dosage forms disclosed therein would be capable of controlled release. As noted above, because Mehra et al. are using a disintegration test, the ordinary artisan at the time of the invention would have a reasonable expectation that the dosage form disclosed therein *would be optimized for immediate release.* In this respect, given the state of the art at the time of the invention (and presently as well), the only way the ordinary artisan would have known to optimize the dosage form of Mehra et al. for controlled release

using disintegration testing would have been by reading the disclosure of the instant application, which, as noted above, is an impermissible hindsight reconstruction. *See, e.g., in re Deuel, supra.*

Because Mehra et al. do not teach or suggest the claimed invention for the reasons set forth above, it follows that Mehra et al. do not render the claimed invention obvious. In view of the foregoing, applicants request withdrawal of this rejection.

THE ANTICIPATION REJECTION OVER FRANZ ET AL.

Claims 1-8, 10-13, 17, 18, and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by Franz et al. (USPN 5,232,704). This rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992).

Independent claims 1 and 17 recite a series of method steps; accordingly, in order for Franz et al. to anticipate the claimed invention, Franz et al. must teach each step of the claimed method.

Franz et al. teach a sustained release capsule including a non-compressed bi-layer formulation that includes a drug release layer and a buoyant or floating layer (col. 2, ll. 43-49), which is designed to delivery prostaglandins (col. 2, ll. 63-65). At col.. 7, ll. 4-12, Franz et al. explain that the cohesion between the two layers of the capsule was tested using disintegration testing. Franz et al. disclose that as expected, during disintegration testing, the drug release layer progressively eroded while the buoyancy layer remained intact for over eight hours (col. 7, ll. 9-12). Franz et al. do ***not*** teach or suggest that the disintegration test was used to correct the *in vivo/in vitro* drug release profiles of the prostaglandin disclosed therein.

In the Office Action of August 30, 2005, the Examiner took the position that Franz et al. was correlating the *in vitro* disintegration test results obtained therein with a desired *in vivo* drug release profile based upon the disclosure at col. 9, ll. 7-21. The Examiner's position is wrong for the reasons that follow.

It is well-known in the art to which the invention pertains that correlation testing is a specific mathematic formula that is used to used to determine an *in vivo* release profile based upon *in vitro* testing (*see*, Chapters 13 and 21 of Wagner). Franz et al. does ***not*** use the disintegration test in this way; the disintegration test of Franz is used merely to determine the rate of disintegration of the two layers of the bilayer capsule. As is clearly disclosed in all of the examples, the pharmacological kinetics of the bilayer capsule are determined using dissolution testing. The reference at col. 7, lines 16-19, regarding the disintegration testing merely notes that those tablets that were found to have the expected disintegration

characteristics of rapid erosion of the drug layer but not the buoyant layer were ***chosen*** fro an *in vivo* investigation. This statement alone does ***not*** teach, suggest, or even remotely approach a disclosure regarding correlation, it merely emphasizes that tablets displaying a certain behavior at disintegration were selected for further testing. As is clear from the examples, the further testing was the dissolution testing described in detail at col. 18, line 51, to col. 22, line 21.

Because Franz et al. uses the disintegration test solely to determine the rate of disintegration of the drug containing layer versus the buoyancy layer and ***not*** as a test to correlate the *in vivo/in vitro* drug release profiles of the drug disclosed therein, it follows that Franz et al. does not anticipate the claimed invention. In view of the foregoing, applicants request withdrawal of this rejection.

THE OBVIOUSNESS REJECTION OVER FRANZ ET AL. IN VIEW OF O'NEIL ET AL.

Claims 1-26 stand rejected under 35 U.S.C. § 103(a) as obvious over Friend et al. in view of Franz et al. (USPN 5,232,704)and O'Neill et al. (USPN 4,704,405). This rejection is respectfully traversed.

Franz et al. is discussed above. The Examiner cites O'Neill for the teaching of a tablet. Because Franz et al. clearly does not teach or suggest the use of disintegration testing to determine *in vivo/in vitro* correlation of drug release, the additional teaching of O'Neill will not serve to correct the deficiencies of Franz et al. Because Franz et al. in view of O'Neill et al. does not teach or suggest the claimed invention, it follows that the claimed invention is not rendered obvious by the hypothetical combination of Franz et al. in view of O'Neill. In view of the foregoing, applicants request withdrawal of this rejection.

OTHER MATTERS

On page 5 of the Office Action, the Examiner acknowledges that claims 1-26 of the instant application have been examined; indeed, the current Office Action and the two previous Office Actions indicate that the Examiner has in fact searched and examined all pending 26 claims of the instant application. Despite the foregoing, in the Office Action under reply, the Examiner requests a discussion on why the claims should not be restricted to two inventions.

As a preliminary matter, applicants submit that because claims 1-26 have already been subject to three Office Actions, thus far, the Examiner has clearly not been subject to a serious burden in examining the 26 pending claims of the application. As applicants have not added new claims or amended the independent claims in such a way that they have become significantly different from their original form, there does not appear to be any reason for the Examiner's sudden interest in claim restriction.

Notwithstanding the foregoing, the Examiner should not restrict the claims of the instant application for the following reasons.

Both the method of claims 1-16 and the method of claims 17-26 include a dosage form comprising a hydrophilic polymer and an active agent incorporated in the hydrophilic polymer, wherein the dosage form is treated in a USP disintegration tester in order to obtain the *in vitro* drug release profile that correlates to a desired *in vivo* drug release profile. The only difference between the method of claims 1-16 and the method of claims 17-26 is the recitation in claim 17 of the features of the hydrophilic polymer; however, because the same hydrophilic polymers are disclosed for both the method of claims 1-16 and the method of claims 17-26, the Examiner should not be searching for different hydrophilic polymers for the two claim sets.

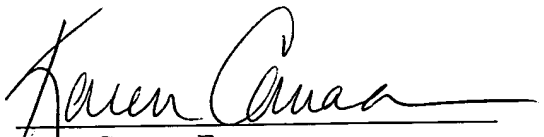
Because no serious burden is imposed upon the Examiner for the continued search and examination of method claims 1-16 and method claims 17-26, applicants respectfully request that the Examiner continue to search and examine all pending claims, i.e., claims 1-26 together in the instant application.

CONCLUSION

With this paper, each of the Examiner's rejections have been fully addressed and overcome. Because there will be no outstanding issues for this matter upon entry of this paper, applicants respectfully request withdrawal of all claim rejections and passage of this application to issue.

Any questions regarding this paper or the application in general may be addressed to the undersigned attorney at 650-251-7713 or kcanaan@mintz.com.

Respectfully submitted,

By: 

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